RECEIVED FEB-26-00 11:04AM FROM- TO- PAGE 40

FEB. 25. 2000 2:13PM No. 6053 P. 40

Surrogate Markers Suitable for Testing

Hans-Juergen Haussmann, Ph.D.,
INBIFO, Cologne, Germany

DRAFT

Discussion Document Prepared by Philip Morris, USA,
for the Institute of Medicine Panel Presentation
3/01/00

PM3006856813

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 41

FEB. 25. 2000 2:13PM No. 6053 P. 41

Presentation Objective

Discuss surrogate markers that are
mechanistically related to and
suitable for testing of
major diseases with cigarette smoke-related mortality

Disease	Cigarette Smoke-Related Mortality in US (1990)
Cancer	151322
Cardiovascular disease	179820
Respiratory disease	84475

(Centers for Disease Control and Prevention, 1993)

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856814

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

Require

Surrogate
reduction

- mecha
- sensit
- reproc

25-Feb-00 HHM IOM - Surro

- Long-term
  - historic att
    - » equivoca
  - recent dev
    - » Lovelace
    - » UC Davi
    - » Philip Mo
- Mouse skir
  - » initiation-
  - » restricted
  - » suitable f
- Short-term

25-Feb-00 HHM IOM - Surrogates

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

Mechanisms Related to Human Lung Cancer Development

- Initiation-promotion paradigm
  - has not been conclusively applied to lung cancer development
  - genotoxic events linked to initiation:
    - » activation of proto-oncogenes
    - » inactivation of tumor suppressor genes
  - reversible morphological changes possibly linked to promotion:
    - » basal cell hyperplasia } { inflammation
    - » squamous metaplasia } { irritation
  - declining lung cancer risk after cessation of smoking indicative of role of promotion

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856816

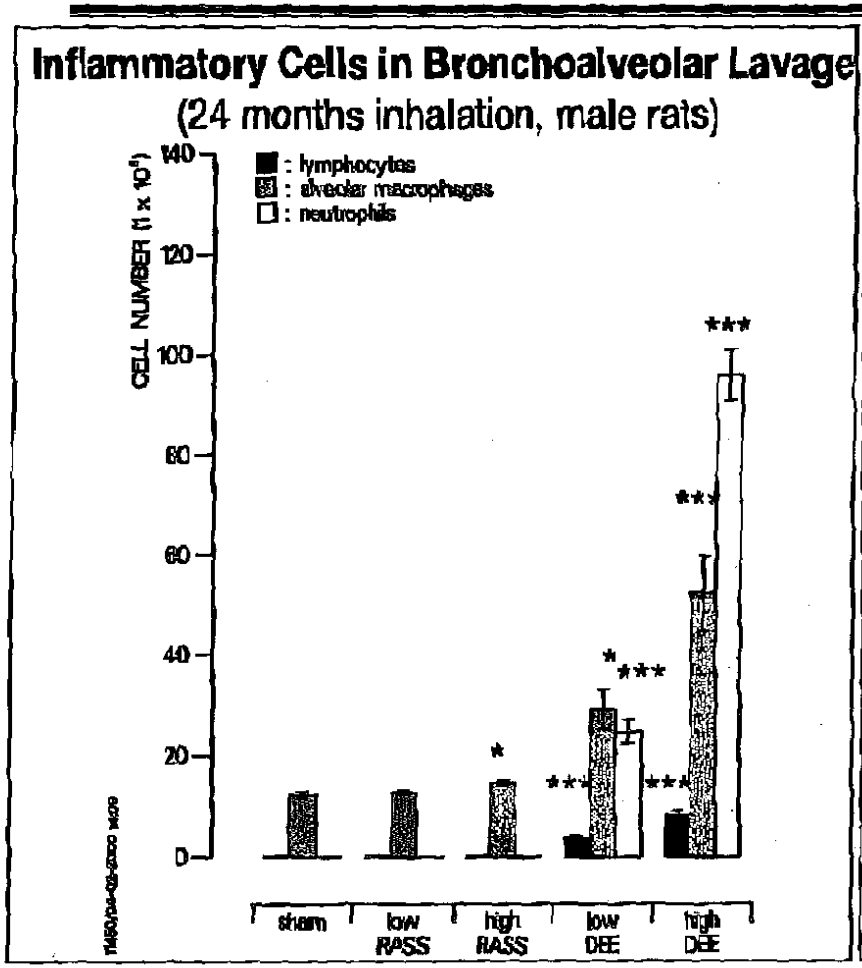
Feb. 23. 2000 2:14PM No. 6053 P. 42

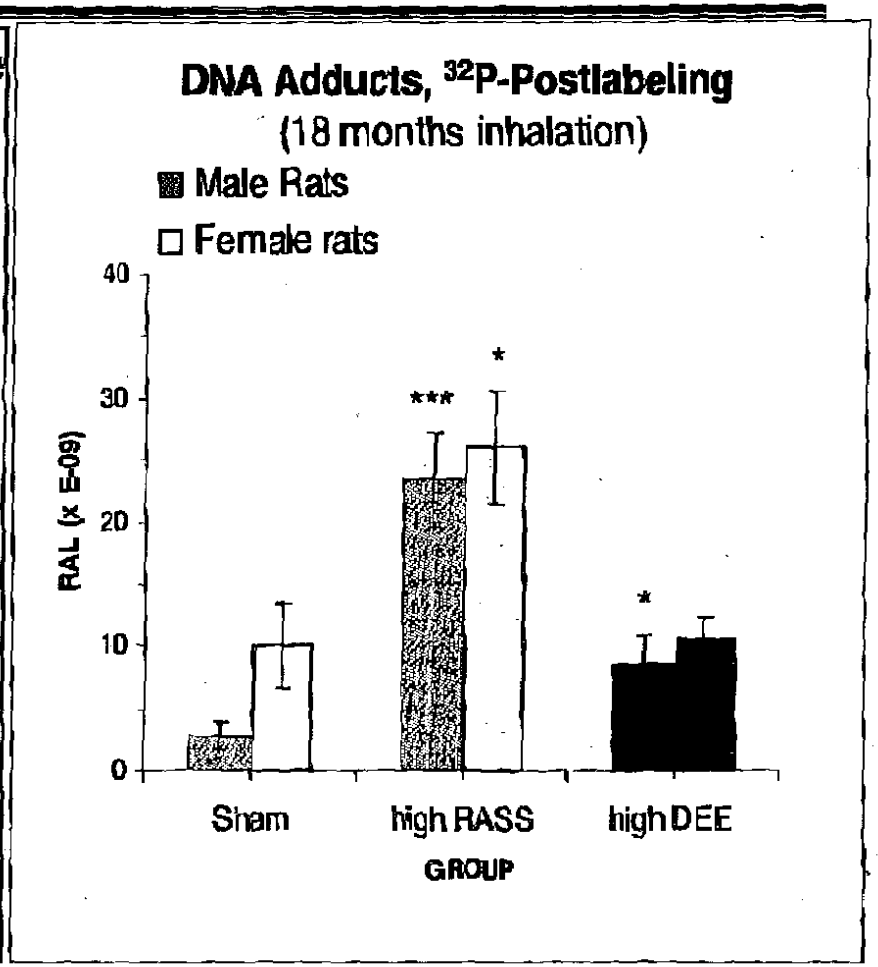
Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 43

FEB. 25. 2000 2:14PM NO. 8053 P. 43

Philip Morris' Mechanistic Rat Inhalation Study on Combustion Aerosols





(RASS: Room-aged sidestream smoke; DEE: Diesel engine exhaust, Hock et al., 1999; Friedrichs et al., 2000)

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

DRAFT

PM3006856817

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

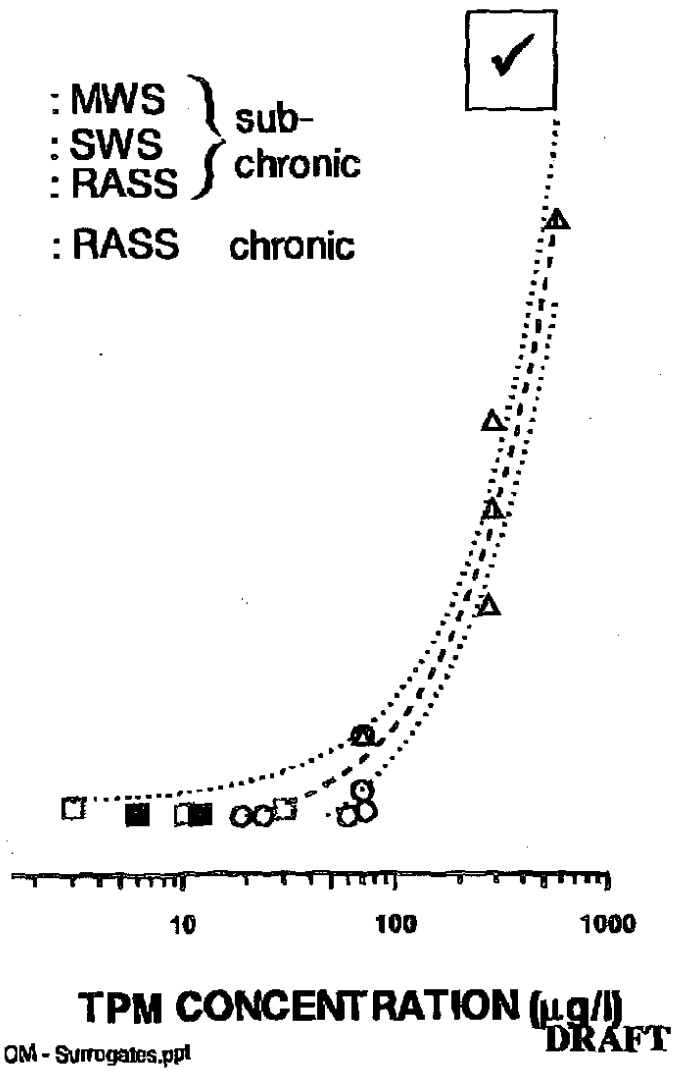
RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 44

Suital
Inhala

25-Feb-00 HHM IOM

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0000

ability of Subchronic Cigarette Smoke ation to Investigate Chronic Bronchitis



- dose-dependent increase of absolute and relative number of inflammatory cells (Mull et al., 1984)
- no progression with prolonged inhalation period (Haussmann et al., 1998)

DRAFT

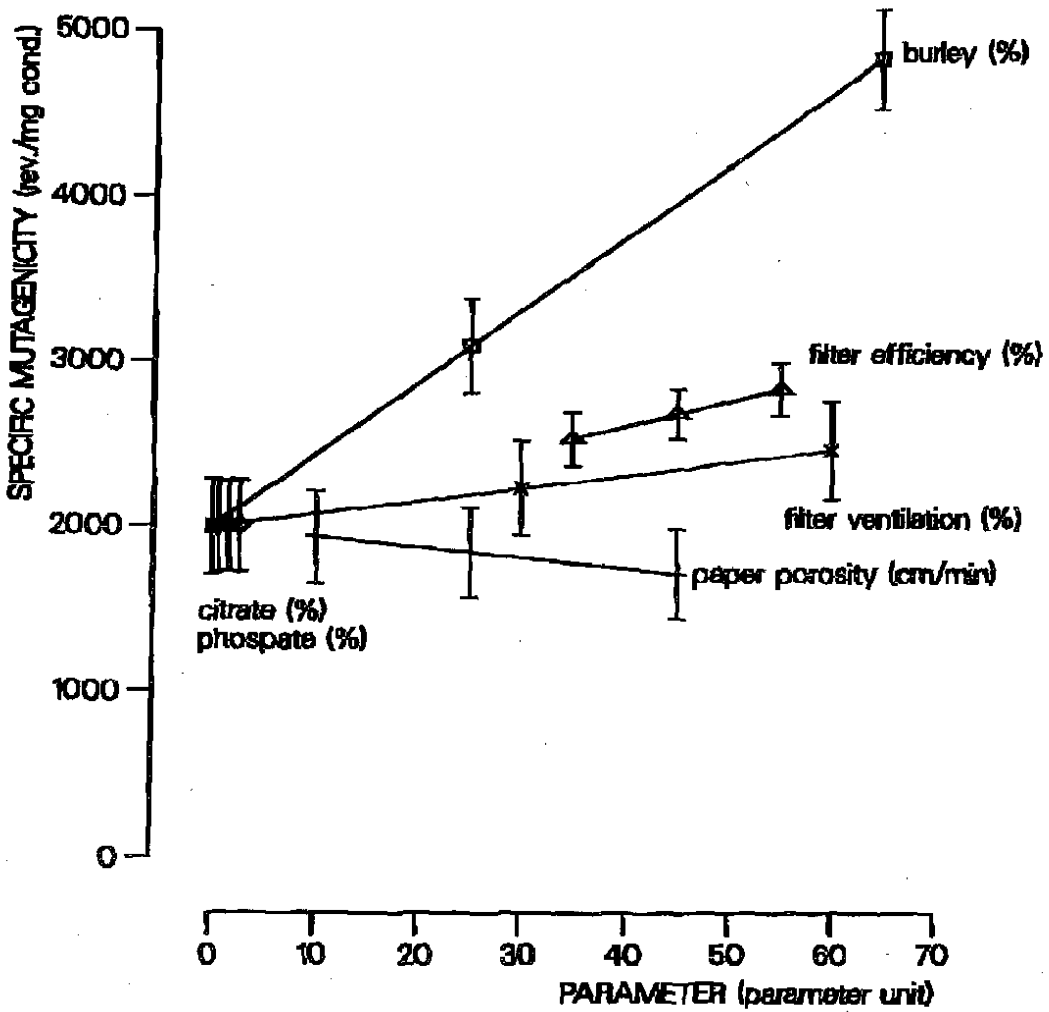
OM - Surrogates.ppt

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856819

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

Suitability of the Bacterial Mutagenicity Assay to Investigate Cigarette Design Parameters



Test conditions:

- » cig. smoke condensate
- » tester strain TA 98, + S9
- » multiple linear regression analysis

(Tewes et al., 1999)

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

DRAFT

PM3006856820

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

Short-Term Experimental Surrogates

Smoke chemistry
- extended towards IARC carcinogens ✓

Two-stage transformation
(Schlage et al., 1999) -

In vitro cytotoxicity ✓

In vitro genotoxicity ✓
- bacterial mutagenicity
- mammalian cell mutagenicity

Initiation **Promotion**

In vivo genotoxicity -
- micronucleus assay
(Lee et al., 1990)

Subchronic inhalation ✓
- irritative changes in respiratory tract

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856821

Feb. 23. 2000 2:14PM No. 6053 P. 44

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 45

FEB. 25. 2000 2:15PM No. 6053 P. 45

Summary

- Carcinogenicity
  - short-term markers ✓
  - skin painting ✓
  - long-term inhalation ?
- Cardiovascular disease
  - ApoE-deficient mouse ?
  - other candidates ?
- Chronic obstructive pulmonary diseases
  - inflammation ✓
  - emphysema in vivo ?

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856822

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 46

FEB. 25. 2000 2:15PM No. 6053 P. 46

Conclusion

The availability of surrogate assays is restricted by the limited understanding of the relevant pathogenic mechanisms of the diseases.

This limitation requires the use of standardized assays as a default. Such are available for carcinogenicity but are lacking for cardiovascular and chronic obstructive pulmonary diseases.

Therefore, we have started programs to address these gaps and would welcome guidance from this committee.

PM3006856823

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 47

Feb. 25. 2000 2:15PM No. 6053 P. 47

Chronic Obstructive Lung Diseases

- Chronic (obstructive) bronchitis
  - mediated by pulmonary inflammation (reversible)
    - » increase of bronchoalveolar inflammatory cells
      - alveolar macrophages
      - polymorphonuclear leukocytes (PMNL)
      - lymphocytes
  - airway obstruction by mucus and morphological changes
- Emphysema
  - irreversible destruction of alveolar walls
    - » disturbance of the protease - anti-protease balance, e.g.,
      - increased elastase activity from inflammatory cells
      - inactivated protease inhibitors

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856824

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 48

Feb. 25. 2000 2:15PM No. 6053 P. 48

Experimental Emphysema Models

- Chronic inhalation of mainstream smoke ?
  (March et al., 1999)
  - morphological changes similar to those seen in man
    - » increase of alveolar septa mean linear intercept
    - » increase of volume density of alveolar air space
    - » decrease of volume density of alveolar septa
    - » accompanied by accumulation of PMNL
- In vitro model for emphysema
  - inactivation of alpha-1-protease inhibitor (Pryor et al., 1990) ✓

PM3006856825

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 49

Feb. 25. 2000 2:15PM No. 6053 P. 49

Limited Understanding of Role of Individual Smoke Constituents in Disease Etiology and Mechanisms

1999 SOT symposium:

Carcinogenicity of Cigarette Smoke: Bridging the Gap between Complex Mixtures and Individual Components

(Burchiel and Witschi)

- *... polycyclic aromatic hydrocarbons and the tobacco-specific carcinogen NNK are the most important compounds in cigarette smoke with respect to lung cancer induction in humans* (Hecht).

⇕

- *A recently developed tobacco smoke lung cancer model in strain A/J mice ... has made it possible to evaluate the effects of tobacco smoke gas phase in comparison with the effects of full tobacco smoke ...* (Witschi)

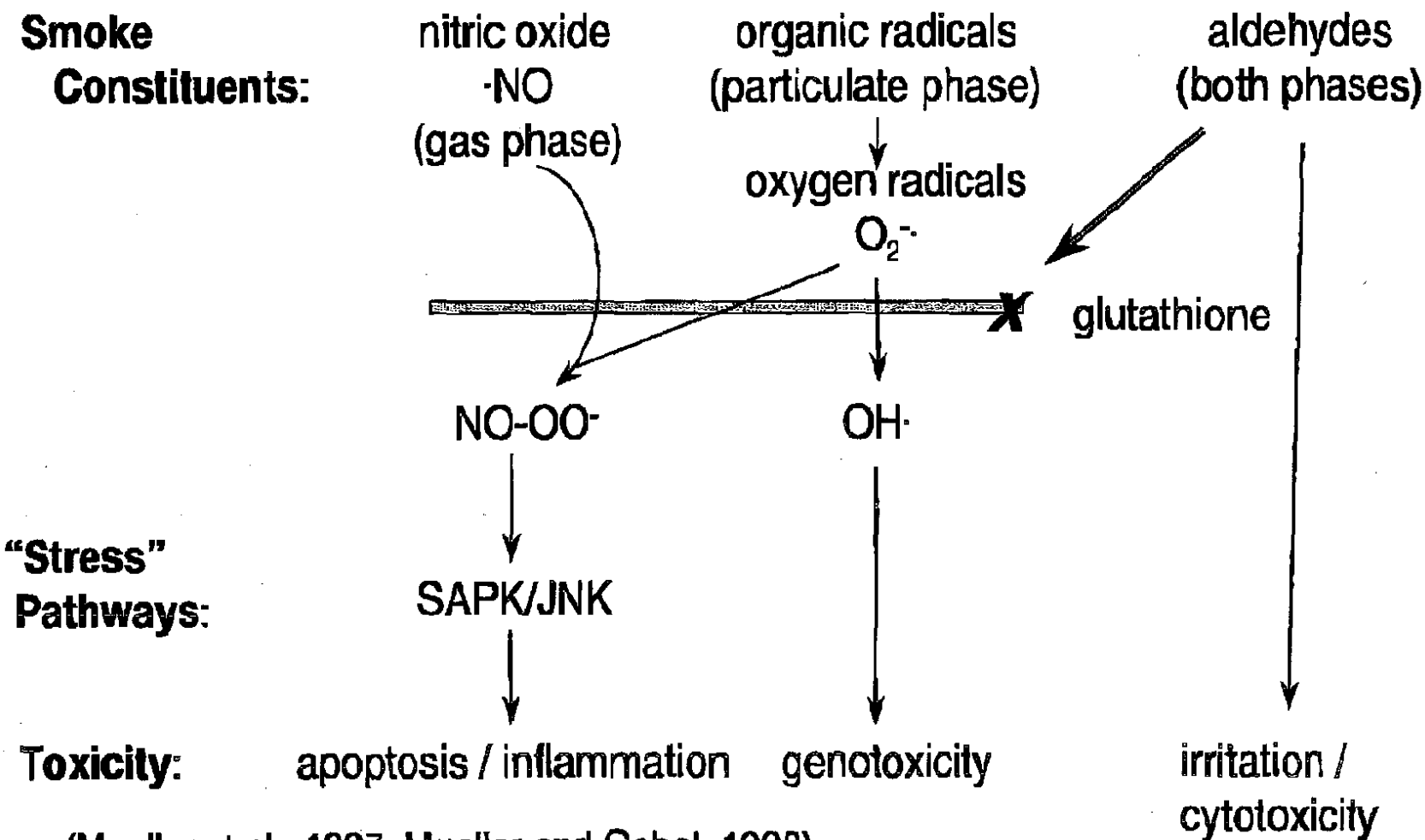
DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856826

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

Intracellular Interactions of Smoke Constituents



(Mueller et al., 1997; Mueller and Gebel, 1998)

25-Feb-00 HHM IOM - Surrogates.ppt

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 51

Feb. 25. 2000 2:16PM No. 6053 P. 51

Short-Term Experimental Surrogates

Smoke chemistry
- extended towards IARC carcinogens

Two-stage transformation
(Schlage et al., 1999)

In vitro cytotoxicity

In vitro genotoxicity
- bacterial mutagenicity
- mammalian cell mutagenicity

Initiation **Promotion**

Subchronic inhalation
- irritative changes in respiratory tract

In vivo genotoxicity
- micronucleus assay
(Lee et al., 1990)

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

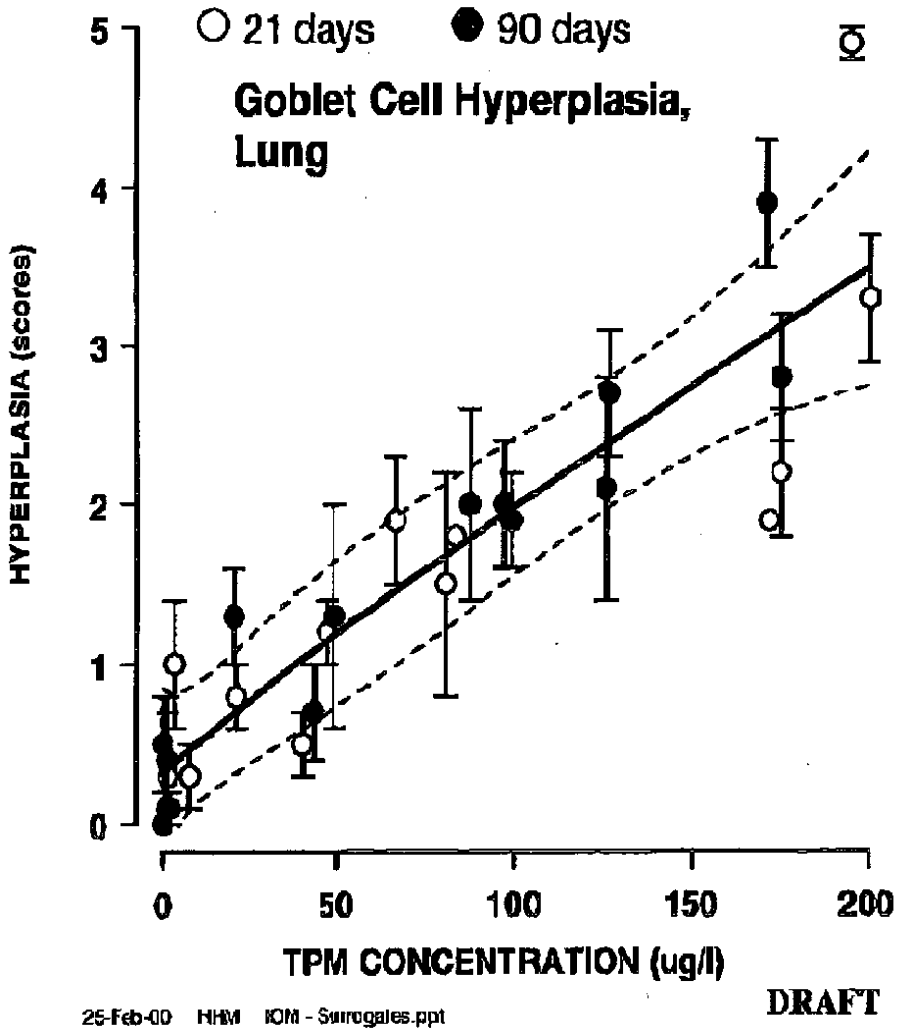
PM3006856828

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 52

Feb. 25. 2000 2:16PM No. 6053 P. 52

Suitability of Subchronic Cigarette Smoke Inhalation to Investigate Morphological Changes in the Rat Respiratory Tract



Morphological changes:

- hyperplasia, squamous metaplasia, atrophy
- dose-dependent (e.g., Vanscheeuwijk et al., 1998)
- consistent throughout respiratory tract (Roemer et al., 1998)
- reversible (e.g., Coggins et al., 1986)
- no progression in chronic studies (Haussmann et al., 1998)

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856829

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 53

Feb. 25. 2000 2:16PM No. 6053 P. 53

Cardiovascular Diseases

- Types
  - coronary heart disease/ischemic heart disease
    - » cardiac ischemia
    - » myocardial infarction
  - cerebrovascular disease
    - » stroke
    - » transient cerebral ischemia
  - peripheral vascular disease
- Mechanisms involved
  - **atherosclerosis**
  - vascular wall changes
  - vascular tone changes
  - coagulopathy

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

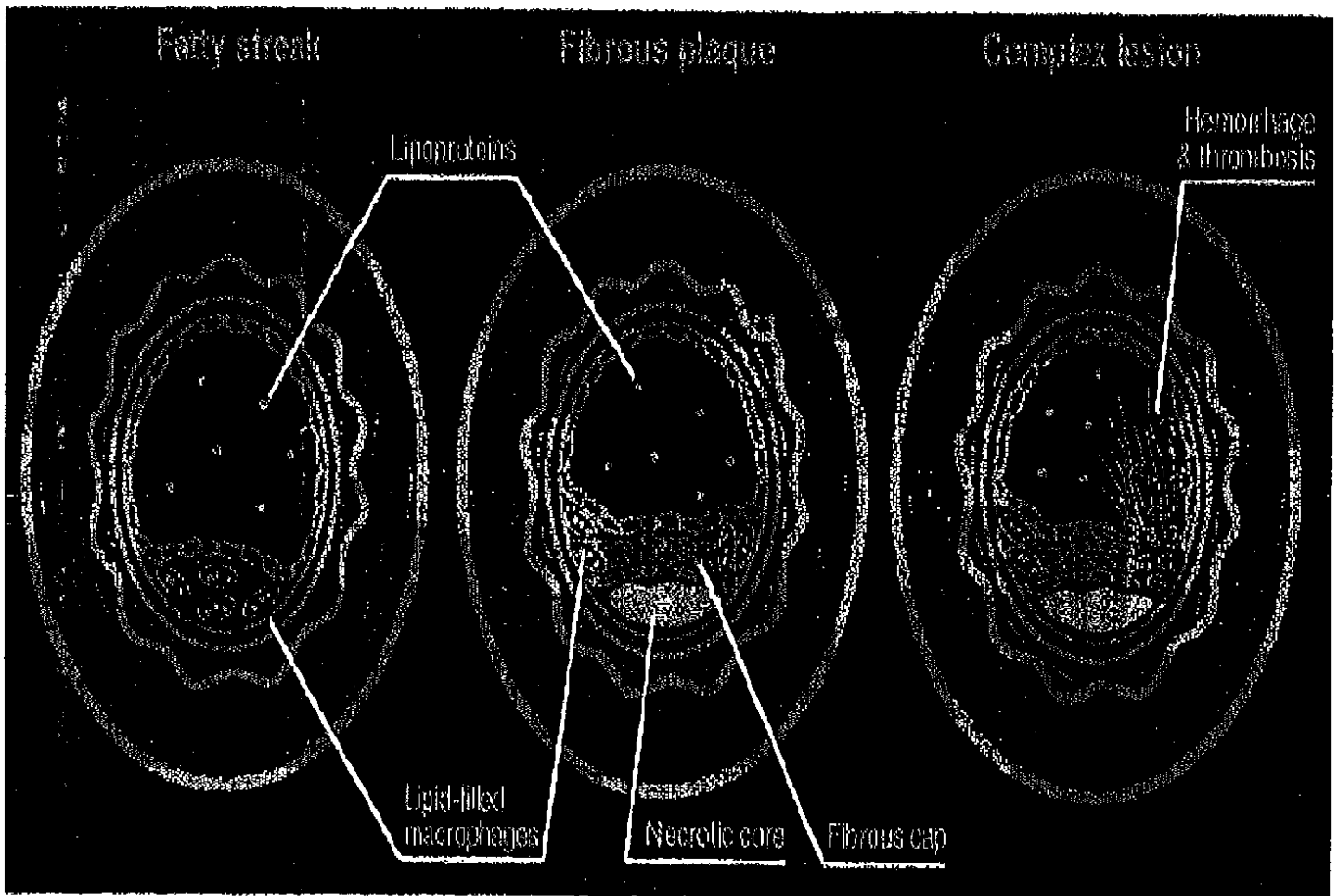
PM3006856830

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 54

Feb. 25. 2000 2:16PM No. 6053 P. 54

The Three Stages of Atherosclerotic Lesion Formation (Breslow, 1996)



Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

DRAFT

PM3006856831

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 55

Feb. 25. 2000 2:17PM No. 6053 P. 55

Experimental Models for Atherosclerosis
(Examples)

- ApoE-deficient mouse
  - atherosclerotic process very similar to human disease in terms of
    - » types and site of lesions (Breslow, 1996)
    - » response to human risk factors, i.e.,
      - high cholesterol / high fat diets
      - cigarette smoke (subchronic inhalation of sidesteam smoke: Gairola and Daugherty, 1999) ?
    - » mechanistic hallmarks
      - lipoprotein oxidation
- Rabbits and birds (cockerels, pigeons)
  - pathogenesis less similar to humans
  - reported to be responsive to cig. sidestream smoke (Zhu et al., 1993; Penn and Snyder, 1993/1996) ?

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856832

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 56

Feb. 25. 2000 2:17PM No. 6053 P. 56

Chronic Obstructive Lung Diseases

- Chronic (obstructive) bronchitis
  - mediated by pulmonary inflammation (reversible)
    - » increase of bronchoalveolar inflammatory cells
      - alveolar macrophages
      - polymorphonuclear leukocytes (PMNL)
      - lymphocytes
  - airway obstruction by mucus and morphological changes
- Emphysema
  - irreversible destruction of alveolar walls
    - » disturbance of the protease - anti-protease balance, e.g.,
      - increased elastase activity from inflammatory cells
      - inactivated protease inhibitors

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856833

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

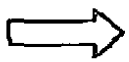
RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 57

Feb. 25. 2000 2:17PM No. 6053 P. 57

Requirements for Suitable Surrogate Markers

Surrogate markers suitable to assess harm reduction need to be

- mechanistically related to the disease,
- sensitive and dose-responsive,
- reproducible and validated.



DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856834

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 58

Feb. 25. 2000 2:18PM No. 6053 P. 58

Experimental Models for Pulmonary Carcinogenesis

- Long-term inhalation studies leading to lung tumors
  - historic attempts:
    - » equivocal, mostly negative, irrespective of rodent species (Coggins, 1997) -
  - recent developments:
    - » Lovelace Respiratory Research Institute studies on rats (Finch et al.)
    - » UC Davis studies on A/J mice (Witschi et al.) ?
    - » Philip Morris' mechanistic study on rats (Stinn et al.)
- Mouse skin painting studies
  - » initiation-promotion model (e.g., Roemer and Hackenberg, 1990)
  - » restricted to particulate phase of cig. Smoke ✓
  - » suitable for specific purposes
- Short-term experimental surrogates

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856835

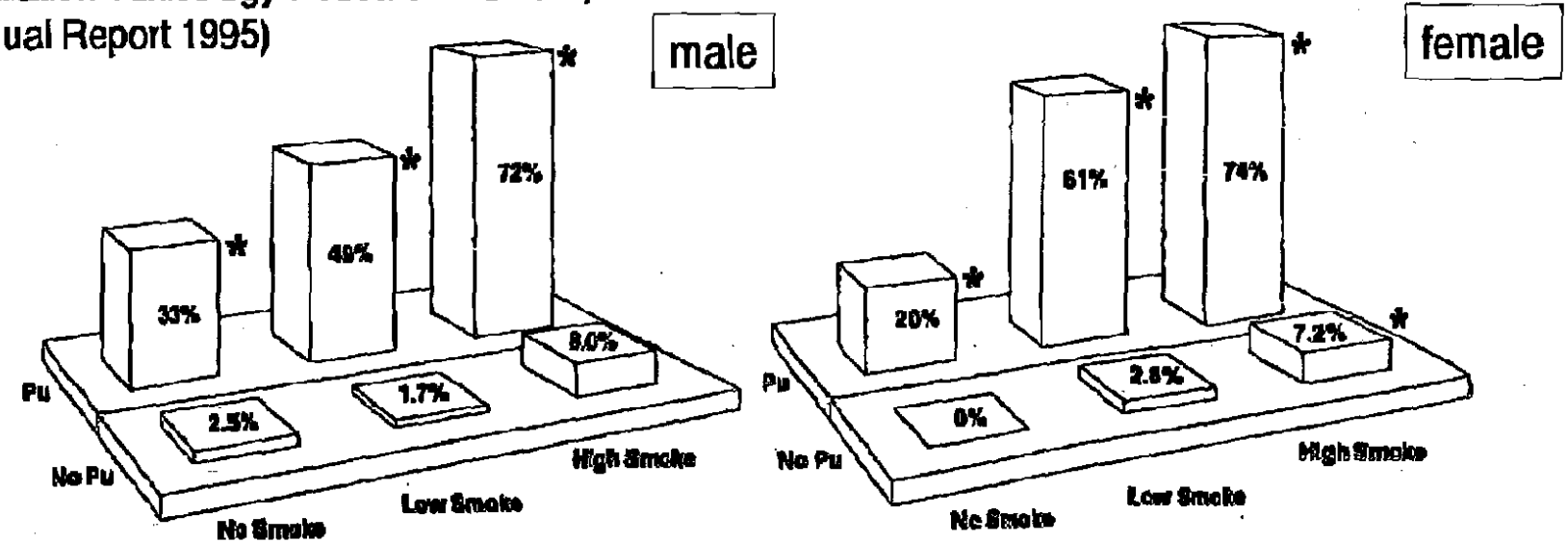
Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 59

Feb. 25. 2000 2:18PM No. 6053 P. 59

Long-Term Rat Inhalation Study on Cigarette Smoke and Plutonium Dioxide

(incidence of lung tumors;
Inhalation Toxicology Research Institute,
Annual Report 1995)



over-additive effect largely due to impairment of plutonium clearance by cigarette smoke inhalation (Finch et al., 1998)

25-Feb-00 HHM IOM - Surrogates.ppt

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856836

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 60

FEB. 25. 2000 2:18PM No. 6053 P. 60

Experimental Models for Pulmonary Carcinogenesis

- Long-term inhalation studies leading to lung tumors
  - historic attempts:
    - » equivocal, mostly negative, irrespective of rodent species (Coggins, 1997) -
  - recent developments:
    - » Lovelace Respiratory Research Institute studies on rats (Finch et al.)
    - » UC Davis studies on A/J mice (Witschi et al.) ?
    - » Philip Morris' mechanistic study on rats (Stinn et al.)
- Mouse skin painting studies
  - » initiation-promotion model (e.g., Roemer and Hackenberg, 1990)
  - » restricted to particulate phase of cig. Smoke ✓
  - » suitable for specific purposes
- Short-term experimental surrogates

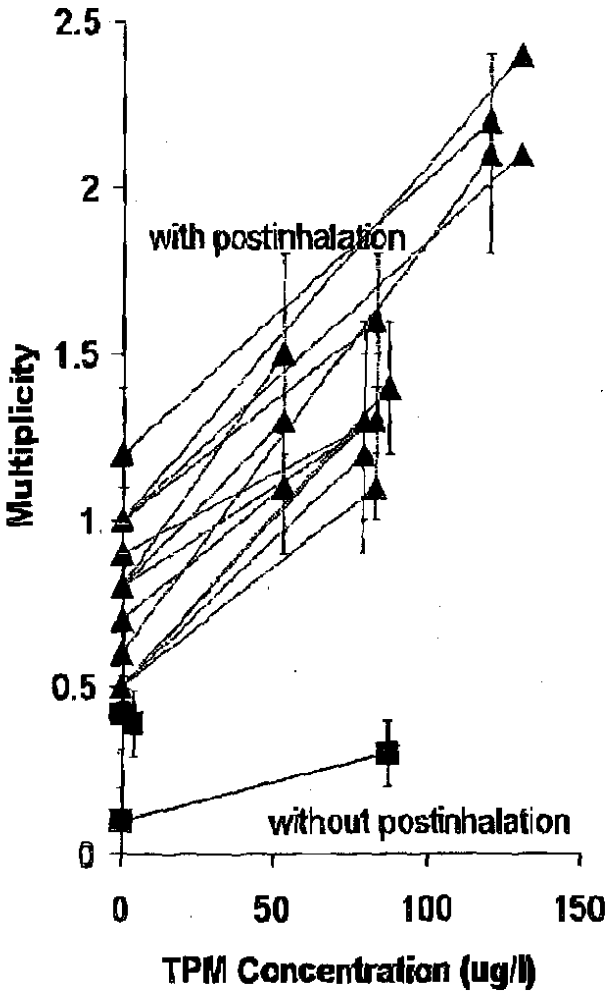
PM3006856837

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 61

FEB. 25. 2000 2:18PM No. 6053 P. 61

Chronic A/J Mouse Inhalation Studies



25-Feb-00 HHM IOM - Surrogates.ppt

- dose-dependent for ETS surrogate (Witschi, 1998/9)
- negative study with mainstream smoke (Finch et al., 1996)
- mechanistic issues
  - » postinhalation phase needed for tumor expression
  - » no morphologic changes except increased tumor multiplicity
  - » filtered smoke as effective

needs to be further evaluated

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856838

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001

RECEIVED FEB-25-00 11:04AM FROM- TO- PAGE 62

FEB. 25. 2000 2:18PM No. 6053 P. 62

Experimental Models for Pulmonary Carcinogenesis

- Long-term inhalation studies leading to lung tumors
  - historic attempts:
    - » equivocal, mostly negative, irrespective of rodent species (Coggins, 1997) -
  - recent developments:
    - » Lovelace Respiratory Research Institute studies on rats (Finch et al.)
    - » UC Davis studies on A/J mice (Witschi et al.) ?
    - » Philip Morris' mechanistic study on rats (Stinn et al.)
- Mouse skin painting studies
  - » initiation-promotion model (e.g., Roemer and Hackenberg, 1990)
  - » restricted to particulate phase of cig. Smoke ✓
  - » suitable for specific purposes
- Short-term experimental surrogates

DRAFT

Discussion Document Prepared by Philip Morris, USA, for the Institute of Medicine Panel Presentation 3/01/00

PM3006856839

Source: https://www.industrydocuments.ucsf.edu/docs/pylx0001